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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/616,082 | 07/08/2003 | Stephen Hamilton | GFI-107 | 9644 |

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| EXAMINER | |
|---|---|
| JOIKE, MICHELE K | |
| ART UNIT | PAPER NUMBER |
| 1636 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/616,082 | HAMILTON, STEPHEN | |
| | Examiner | Art Unit | |
| | Michele K. Joike, Ph.D. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-16, 18-30, 57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-16,18-30,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 21, 2007 has been entered.

Claims 1, 2, 4-16, 18-30, 57 and 58 are examined.

### *Priority*

**§ 1.78 Claiming benefit of earlier filing date and cross-references to other applications.**

(a)

(1) A nonprovisional application or international application designating the United States of America may claim an invention disclosed in one or more prior-filed copending nonprovisional applications or international applications designating the United States of America. In order for an application to claim the benefit of a prior-filed copending nonprovisional application or international application designating the United States of America, each prior-filed application must name as an inventor at least one inventor named in the later-filed application and disclose the named inventor's invention claimed in at least one claim of the later-filed application in the manner provided by the first paragraph of 35 U.S.C. 112. In addition, each prior-filed application must be:

37 CFR 1.78. Applicant is only granted the benefit of priority for US application 10/371,877. The applicant is not listed as an inventor in the other priority documents.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 5, 7, 9, 16, 18-22, 24-30, 57 and 58 are rejected under 35 U.S.C. 102(e) as being anticipated by US 7,029,872. Note: Although Applicant is claiming priority to this patent, Applicant is not being granted benefit of priority since the Applicant is not listed as an inventor on that patent, and the inventor listed on US 7,029,872 is not listed on the instant application. Therefore, there is no inventor in common.

Applicant claims a method for producing a recombinant glycoprotein in a uni- or multicellular fungal cell that does not display alpha-1,6 mannosyltransferase activity. The method further comprises introducing a mannosidase (capable of hydrolyzing at least 10% of the Manα 1,3 and 1,6 linkages of an oligosaccharide), having optimal activity in the Golgi. The enzyme can have a domain having optimal activity from about pH 5.0 to about pH 8.0 and be fused to a cellular targeting signal peptide, and the domain can be endogenous or heterologous. The enzyme can be a class II mannosidase. The signal sequence can be native or heterologous. An N-glycan structure produced is $Man_5GlcNAc_2$, or $GlcNAcMan_3GlcNAc_2$. Specifically, the host cell

can be *Pichia pastoris*. The N-glycan produced should be at least 10 mole %. After the glycoprotein is produced in the cell, it may be isolated. The glycoprotein produced can be a therapeutic protein, including erythropoietin, cytokines such as interferon-.alpha., interferon-.beta., interferon-.gamma., interferon-.omega., and granulocyte-CSF, coagulation factors such as factor VIII, factor IX, and human protein C, soluble IgE receptor .alpha.-chain, IgG, IgM, urokinase, chymase, and urea trypsin inhibitor, IGF-binding protein, epidermal growth factor, growth hormone-releasing factor, annexin V fusion protein, angiostatin, vascular endothelial growth factor-2, myeloid progenitor inhibitory factor-1, and osteoprotegerin.

Note: A. "About" The term "about" used to define the area of the lower end of a mold as between 25 to about 45% of the mold entrance was held to be clear, but flexible. Ex parte Eastwood, 163 USPQ 316 (Bd. App. 1968). Similarly, in W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), the court held that a limitation defining the stretch rate of a plastic as "exceeding about 10% per second" is definite because infringement could clearly be assessed through the use of a stopwatch. MPEP 2173.05 (b).

US 7,029,872 (specifically columns 6-11, 13, 16, 20, Ex. 3 and claim 1) teaches a method for producing a recombinant glycoprotein in a uni- or multicellular fungal cell that does not display alpha-1,6 mannosyltransferase activity. The method further comprises introducing an alpha-1,2 mannosidase (capable of hydrolyzing Manα 1,3 and 1,6 linkages), having optimal activity in the Golgi. The enzyme can have a domain having optimal activity between pH 5.1 and 8.0 and be fused to a cellular targeting

signal peptide, and the domain can be endogenous or heterologous. (Applicants are claiming a pH level from about 5.0 to about 8.0. About 5.0 can be 5.1, when the pH level is given the flexibility as described above in MPEP 2173.05 (b).) The signal sequence can be selected from the host organism as well as from other related or unrelated organisms. An N-glycan structure produced is $Man_5GlcNAc_2$. (Table 6 lists other desired structures produced, such as $GlcNAcMan_3GlcNAc_2$.) Specifically, the host cell can be *Pichia pastoris*. The N-glycan produced should have a high yield, above 30%. Since the production of a high yield of N-glycan structures are taught, it is inherent that at least 10% of the 1,3 and 1,6 Manα linkages are hydrolyzed. After the glycoprotein is produced in the cell, it may be isolated and analyzed. The glycoprotein produced can be a therapeutic protein, including erythropoietin, cytokines such as interferon-.alpha., interferon-.beta., interferon-.gamma., interferon-.omega., and granulocyte-CSF, coagulation factors such as factor VIII, factor IX, and human protein C, soluble IgE receptor .alpha.-chain, IgG, IgM, urokinase, chymase, and urea trypsin inhibitor, IGF-binding protein, epidermal growth factor, growth hormone-releasing factor, annexin V fusion protein, angiostatin, vascular endothelial growth factor-2, myeloid progenitor inhibitory factor-1, and osteoprotegerin.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-16, 18-30, 57 and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for $Man_5GlcNAc_2$, does not reasonably provide enablement for $GlcNAcMan_5GlcNAc_2$. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

*Nature of the invention:* The nature of the invention is claims a method for producing a recombinant glycoprotein in a uni- or multicellular fungal cell that does not display alpha-1,6 mannosyltransferase activity and which produces N-glycans $Man_5GlcNAc_2$ or $GlcNAcMan_5GlcNAc_2$. The method further comprises the host cell containing a mannosidase to hydrolyze an oligosaccharide substrate to produce one or more desired N-glycans.

*Breadth of the claims:* The claims are broad because production of any desired N-glycan is claimed.

*Guidance of the specification:* The specification teaches that $Man_5GlcNAc_2$ and $GlcNAcMan_5GlcNAc_2$ are not native to fungi (see Figure 1A and 1B) and that GlcNAc transferase I is required to produce $GlcNAcMan_5GlcNAc_2$ from $Man_5GlcNAc_2$. There is

no mention of GlcNAc transferase I in the claims.

*Predictability and state of the art:* It is known in the art that GlcNAc transferase I is required to produce $GlcNAcMan_5GlcNAc_2$ from $Man_5GlcNAc_2$. (US 7,029,872, column 11, lines 4-28). The first step involves the selection or creation of a lower eukaryote that is able to produce a specific precursor structure of $Man_5GlcNAc_2$, which is able to accept in vivo GlcNAc by the action of a GlcNAc transferase I. This step requires the formation of a particular isomeric structure of $Man_5GlcNAc_2$. This structure has to be formed within the cell at a high yield (in excess of 30%) since all subsequent manipulations are contingent on the presence of this precursor. $Man_5GlcNAc_2$ structures are necessary for complex N-glycan formation. It is the formation of a particular, GlcNAc transferase I accepting intermediate (Structure I) in high yield (above 30%), which is required. The formation of this intermediate is necessary and subsequently allows for the in vivo synthesis of complex N-glycans.

*Amount of experimentation necessary:* No experimentation is required if GlcNAc transferase I is introduced into the cell, otherwise, the level of experimentation is high to find another enzyme to replace GlcNAc transferase I to catalyze the reaction of $Man_5GlcNAc_2$ to $GlcNAcMan_5GlcNAc_2$ to produce other N-glycans.

***Allowable Subject Matter***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele K. Joike, Ph.D. whose telephone number is 571-272-5915. The examiner can normally be reached on M-F, 9:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nancy T. Vogel/
Primary Examiner, Art Unit 1636

Michele K Joike, Ph.D.
Examiner
Art Unit 1636